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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/455,952	12/07/99	MICHALOPOULOS G	A32516

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HM12/0926

EXAMINER	
NAFF, D	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 09/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/455952	Michalopoulos et al
Examiner	Group Art Unit
Natt	1651

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 7/19/01.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-19 is/are pending in the application.

Of the above claim(s) 8-11, 13 + 15-19 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-7, 12 + 14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosur Statement(s), PTO-1449, Paper No(s). 4 Filed 7/31/00

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

In a response of 2/19/01 to a restriction requirement of 2/14/01, applicants elected Group I (claims 1-7, 12 and 14).

Claims 8-11, 13 and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7 (filed 7/19/01).

Claims examined on the merits are 1-7, 12 and 14.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1 wherein hepatocytes and nonparenchymal cells of the co-culture are obtained by perfusion of liver tissue with collagenase to obtain isolated hepatocytes having 3% contamination with nonparenchymal cells, and for the population of matrix/hepatic cell clusters of claim 14 being obtained by this method, does not reasonably provide enablement for another method of providing a combination of hepatocytes and nonparenchymal cells for co-culturing as claimed, and for obtaining the population of matrix/hepatic cell clusters of claim 14 by another method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

No enabling description has been provided of how to obtain a combination of hepatocytes and nonparenchymal cells for co-culture as claimed other than as described in the specification at page 24, lines 9-12, and of how to produce the population of matrix/hepatic cell clusters of claim 14 other than by carrying out the method of claim 1 when obtaining the combination of hepatocytes and nonparenchymal cells as set forth above.

If the cells of the co-culture are not obtained from liver tissue to produce isolated hepatocytes containing 3% of nonparenchymal cells, proliferated hepatocytes will not be obtained having useful hepatic function. Too many or too few nonparenchymal cells would result in the hepatocytes not proliferating properly to produce a bio-artificial liver or a hepatic cell culture suitable for implanting to provide hepatic function. Nonparenchymal cells present in an amount substantially higher than 3% would result in too few hepatocytes present after culturing to provide adequate hepatic function. Nonparenchymal cells present in an amount substantially less than 3% would result in the nonparenchymal cells having no affect on proliferation of the hepatocytes. If the population of claim 14 is not produced as set forth by the method, the population will not be capable of acceptable hepatic function for uses described in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "nonparenchymal cells" is uncertain as to meaning and scope. The specification has not provided a sufficiently definite and precise definition of this negative term to enable one to know when cells used are parenchymal and nonparenchymal. The specification (page 24, lines 9-12) defines nonparenchymal cells only in terms of how they are obtained as a 3% contaminate when isolating hepatocytes from liver tissue by a collagenase perfusion technique.

Claim 1 in the last line is unclear as to the relationship of the hepatocytes that retain hepatic function to the hepatocytes cultured in line 2. If the hepatocytes are the same, the last line should be changed to read -- the hepatocytes while retaining hepatic function of the hepatocytes --.

In claim 14, the meaning and scope of matrix/hepatic cell clusters is uncertain. It is uncertain as to whether the hepatic cell or matrix or both form the clusters, and the shape that is a "cluster" is uncertain. How are clusters formed by hepatocytes and nonparenchymal cells being associated with a matrix coated with a biologically active molecule?

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-7, 12 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Michalopoulos et al (Hepatology (1999)).

The claims are drawn to a method of generating a hepatic cell culture by co-culturing hepatocytes and nonparenchymal cells in the presence of growth factors and a matrix coated with at least one biologically active molecule that promotes cell adhesion, proliferation or survival under conditions sufficient to allow for the proliferation of the hepatocytes while retaining hepatic function of the hepatocytes. Also claimed (claim 14) is a population of matrix/hepatic cell clusters.

Michalopoulos et al disclose a method of co-culturing hepatocytes and nonparenchymal cells as claimed. A population of matrix/hepatic cell clusters as required by claim 14 inherently results from the method of Michalopoulos et al.

Michalopoulos et al containing the present joint inventors as co-authors does not make Michalopoulos et al unavailable as prior art since Michalopoulos et al contains five additional co-authors who are not inventors.

Claims 1-7, 12 and 14 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The Michalopoulos et al reference describes the presently claimed invention, and contains five co-authors in addition to the present joint inventors. This indicates that the present invention resulted from a joint inventorship different from the present joint inventorship.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-7, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitaka et al (Hepatology 1999) in view of Naughton et al (5,624,840) and Vacanti et al (5,759,830).

The invention is described above.

Mitaka et al disclose obtaining hepatic cells and nonparenchymal cells from liver tissue and culturing the hepatic cells and nonparenchymal cells together for hepatic organoid reconstruction.

Naughton et al disclose growing stromal cells on a three-dimensional matrix such as made from nylon or polystyrene (col 8, line 1) which may be coated with collagen (col 8, line 8) to form a three-dimensional stromal matrix (col 8, lines 30-40), and then growing hepatocytes on the

stromal matrix to form tissue having liver function (col 11, lines 54-57).

Vacanti et al disclose growing hepatocytes (col 6, line 28) in a three-dimensional fibrous scaffold to form tissue having liver function for implanting (col 5, line 35 to col 6, line 62, and col 12, lines 17-47). The fibers of the scaffold may be coated with collagen to enhance cell attachment (col 10, lines 44-47), and epithelial cells may be attached to the scaffold in combination with the hepatocytes (col 12, lines 25-27).

It would have been obvious to carry out the culturing of hepatic cells and nonparenchymal cells together as disclosed by Mitaka et al on a three-dimensional matrix or scaffold as suggested by Naughton et al and Vacanti et al to obtain the function of the matrix or scaffold in producing tissue having liver function. The claims do not exclude the matrix containing stromal tissue as disclosed by Naughton et al. Moreover, it would have been obvious to grow hepatocytes directly on the matrix without first forming stromal tissue when the function of stromal tissue is not needed, and since it is clear from Vacanti et al that stromal tissue can be omitted.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1, 2, 4-7, 12 and 14 above, and further in view of Matsui et al (5,298,615).

The claim requires the matrix to be in the form of polystyrene beads.

Matsui et al disclose that it is standard procedure to culture animal cells on microcarriers such as polystyrene beads coated with collagen (col 2, lines 10-25).

When using a matrix or scaffold as suggested by Naughton et al and Vacanti et al to culture the cells of Mitaka et al as set forth above, it would have been obvious to provide the matrix or scaffold in the form of polystyrene beads coated with collagen as suggested Matsui et al disclosing the use of such beads as being a standard technique for culturing animal cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1657

DMN
9/25/01